administration of an antagonist compound. The Examiner asserts that the method of treating tardive dyskinesias [or for that matter neurological disorders] comprising administration of an antagonist compound allegedly taught by Arnold et al. would necessarily operate by the same biological mechanism of action for treatment of dyskinesias associated with dopamine agonist therapy. The Examiner has asserted that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention form the prior. The Examiner also stated that if the prior art structure is capable of performing the intended use then it meets the claim. The Examiner further stated that in a claim drawn to "a process of making" the intended use must result in a manipulative difference as compared to the prior art.

Applicant respectfully traverses. Contrary to the Examiner's characterization, Arnold et al. does not disclose treatment of dyskinesias associated with dopamine agonist therapy. Arnold et al. specifically recites only tardive dyskinesias (Column 3) that can be allegedly treated by the compounds of formula I therein indicated to be AMPA receptor antagonists, not dyskinesias generally. Applicants have provided evidence that tardive dyskinesias are a different indication than dyskinesias associated with dopamine agonist therapy. If what the Examiner argues as explained above is true, then no claims to newly discovered methods of treating an indication using an already known compound would be deemed patentable. This is clearly not the case. 35 USC 101 provides that whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, . . . , may obtain a patent therefore . . . (emphasis added). Methods of using already known compounds for treatment of indications for which such compounds was not previously known or obvious to be useful are clearly allowable. In view of this, applicants respectfully request that the Examiner withdraw the rejection over Arnold et al.

The Examiner also maintained that claims 1-3 and 5-7 are obvious under 35 USC 103(a) over Klockgether et al. The Examiner asserts that applicants have argued that Klockgether et al. only discusses side effects that might have been observed with the AMPA drug without addressing L-dopa side effect. The Examiner also states that applicants' position that one might expect from Klockgether et al. that administration of NBQX might exacerbate the dyskinesia side effect of l-dopa is not persuasive.

Applicants respectfully traverse. The Examiner has not addressed applicants' arguments in their entirety. Klockgether et al. does not state at page 720, first column, lines 8-10, that NBQX (the AMPA receptor antagonist) reduces and/or eliminates side effects

associated with the administration of l-dopa. The reference merely states at the cited portion, "no NBQX-related side effects (dyskinesias, vomiting, or apparent psychological disturbance) were seen in either monkey". Thus, all that is stated is that the AMPA receptor antagonist, NBQX, did not present any side effects. Nothing here is mentioned or implicated about reducing or eliminating l-dopa side effects. Granted, one of the monkeys (referred to as monkey No. 920) to which the cited statement refers was a monkey with experimentally-induced Parkinson's disease which had been administered NBQX in combination with l-dopa. However, the l-dopa was administered at a dose that had alone produced only marginal improvement [in reducing parkinsonian symptoms] (see page 719, second column, the last three lines, of Klockgether et al.). There is no mention in Klockgether et al. that this monkey ever exhibited side effects due to the l-dopa administration. In fact, there is no mention that this monkey exhibited any side effects.

Klockgether et al. does indicate that this monkey "had severe parkinsonian rigidity in the left upper extremity" caused by the experimentally-induced Parkinson's disease (not either NBQX or l-dopa) (page 719, second column, the last paragraph, which continues on page 720). Klockgether et al. indicates that subsequent to a low dose of NBQX combined with a dose of L-dopa that that had produced marginal improvement, the monkey was able to open its left hand for the first time since receiving the initial parkinsonian-inducing MPTP injection (pages 719-720). As discussed and supported in applicants' previous response, rigidity is a clinical feature of Parkinson's disease. However, "rigidity" is not associated with dopamine agonist therapy, which is recited in the claims of the subject application. Hence, the monkey No. 920 never exhibited any symptoms of l-dopa side effects.

At most, Klockgether et al. suggests that an AMPA receptor antagonist, NBQX, can be combined with dopamine agonist therapy to treat the symptoms of Parkinson's disease, but it does not suggest that an AMPA receptor antagonist could be used for treatment of the effects of dopamine agonist therapy, such as dyskinesias associated with dopamine agonist therapy.

Applicants furthermore maintain that Klockgether et al. suggests that use of an AMPA receptor antagonist might actually result in dyskinesia such as those observed in chronic dopamine replacement therapy, e.g. dystonias and choreic dyskinesias. Klockgether et al. also suggests that use of an AMPA receptor antagonist might actually aggravate such dyskinesias brought about by l-dopa therapy. It is noted that Klockgether et al. states that "[t]he principal findings of this research are that the selective AMPA receptor antagonist

NBQX has potent antiparkinsonian effects in monoamine-depleted rats and MPTP-treated monkeys and that it potentiates the actions of L-dopa". Since NBQX is thus implicated in Klockgether et al. to have effects such as those produced by L-dopa, e.g. reduction in severe rigidity that is symptomatic of Parkinson's disease, it would seem to follow that NBQX might be expected to have the same side effects, e.g. choreic dyskinisias and dystonias, brought about by L-dopa therapy.

The Examiner has noted that Klockgether et al. states, "NBQX did not produce apparent side effects *at the doses tested*" (emphasis added). However, this statement provides no insight or implication as to what effect NBQX would have at other doses or when chronically administered. In contrast, in the specification of the subject application (Example 1) demonstrates that an AMPA receptor antagonist can reduce dyskinesias induced in a monkey by dopamine agonist administration (L-dopa and PHNO).

The Examiner noted that Klockgether et al. states on page 723 that "[s]elective AMPA receptor antagonists have recently been reported to prevent neurotoxicity of L-dopa in an in vitro test system, and that they may therefore prevent some long term adverse effects of L-dopa treatment". This statement mentions neither "treatment" nor "dyskinesia associated with L-dopa therapy". It therefore does not render obvious use of an AMPA receptor antagonist to treat dyskinesia associated with dopamine agonist therapy, as claimed herein. Klockgether et al. provides no assertion or suggestion that neurotoxicity is relevant to dyskinesias which are observed in patients treated with a dopamine agonist. There is no evidence that dyskinesias are related to neurotoxicity.

In view of the above, applicants respectfully request that the Examiner reconsider and withdraw the rejection over Klockgether et al.

The Examiner also maintained that claims 1-3 and 5-7 are obvious under 35 USC 103(a) over Stella et al. in view of Klockgether et al. The Examiner asserted that applicants have argued that Stella teaches that dyskinesias resulting from l-dopa treatment are limited to NMDA receptor antagonists and that any glutamate antagonist other than an NMDA antagonist can be used against dyskinesias induced by l-dopa treatment. The Examiner also asserted that applicants have argued that Klockgether et al. does not compensate for such deficiency, because it was published prior to Stalla et al. and merely demonstrates that AMPA receptor antagonists were available prior to the Stella et al. reference.

However, this is not the gist of applicants' arguments in their previous Communication, and applicants maintain their traversal of the rejection over Stella et al. in

view of Klockgether et al. Klockgether et al. does not state that an AMPA receptor antagonist is a glutamate antagonist. The discussion in Stella et al. regarding dyskinesia produced by levodopa/benserazide therapy is restricted to NMDA receptor blockade. Klockgether et al. does not compensate for this deficiency because Klockgether et al. does not suggest that an NMDA receptor antagonist can be replaced with an AMPA receptor antagonist with the expectation of producing the same effect. Contrary to the Examiner's assertion, applicants have not argues the references separately. In that regard, column 2 of page 1 of Klockgether et al., suggests if anything differences between AMPA antagonism and NMDA antagonism. More particularly, Klockgether et al. states at column 2 of page 1 that l-glutamate antagonists acting at the NMDA receptor have thus far been ineffective as anti-parkinson agents when administered systemically to primates. Klockgether at al. further states that since AMPA receptors are enriched in the subthalamic nucleus in comparison to NMDA receptors, AMPA antagonists may be effective in reducing activity of neurons in the STN. Accordingly, applicants maintain that it is not obvious from Stella et al. in view of Klockgether et al. to treat dyskinesia associated with dopamine agonist therapy using an AMPA receptor antagonist.

In the May 21, 2001 Office Action, the Examiner rejected claims 1-8 under the doctrine of obviousness-type double patenting over U.S. Patent 6,136,812. The Examiner stated that a terminal disclaimer in compliance with 37 CFR 1.321 may be used to overcome this rejection. Applicants will consider filing such a Terminal Disclaimer to advance the prosecution of this case upon indication that the claims of the subject application are otherwise allowable.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, the Examiner is kindly invited to telephone applicants' undersigned attorney at the telephone number provided below.

No fee, other then the fee for the three month extension authorized in the petition filed currently herewith, is believed necessary for filing the subject Communication. However, should any additional fee be determined necessary, authorization is given to charge such fee to Deposit Account No. 16-1445.

Respectfully submitted,

Date: November 21, 2001

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